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Brief Communication

Estimating the Risks for Offspring of First-Cousin Matings. An Approach

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INTRODUCTION

Genetic counselors are sometimes asked about the risks of increased morbidity and mortality among offspring of first-cousin matings, but for most populations of the Western world, data are scanty and inconsistent [1, 2]. This is partly because such matings are rare (except in certain special populations that may not be representative) and difficult to ascertain in an unbiased way. In particular, there are few data on the risk of first cousins having a child with a recognizable, recessively inherited disease, since most studies do not present data in a form permitting analysis in this way.

Most genetic counselors, however, have records of numerous sibships in which the parents are consanguineous and ascertained through the birth of an affected child. Since these are not representative of the consanguineous matings, they are generally not used for studies of the effects of consanguinity. However, it occurred to us that these children would represent an almost unbiased sample of the offspring of first-cousin matings with respect to the frequency of conditions *other than* that through which they were ascertained. The fact that one of the common grandparents was carrying a gene for albinism, for example, which became homozygous in a grandchild, should not influence the probability that these grandparents might carry any other recessive mutant gene. The sample would be unrepresentative insofar as the parents had each produced at least one child, but this bias would not apply to most of the questions we are posing. Using this approach, we conducted a pilot study on the families recorded in the files of this department.

MATERIALS AND METHODS

Fifty-eight probands, ascertained because they had a disorder of genetic interest and parents who were first cousins, were chosen from our files; their families represent the

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"first-cousin" sample. Each proband was matched with a control who had the same disorder, sex, and year of birth but nonconsanguineous parents; their families represent the "control" sample. The same procedure was followed for 27 families in which the parents were second cousins and their controls. Data on the sibs were usually obtained from the mother by a trained interviewer. Causes of morbidity and mortality were confirmed from medical records where possible but otherwise recorded in the informant's words.

The probands of the first-cousin sample were ascertained through disorders with definite (17) or probable (11) autosomal recessive inheritance; autosomal dominant inheritance (2); a chromosomal (1), multifactorial (17), or infectious (1) etiology; or multiple malformations (6). The second-cousin sample had a similar spectrum of disorders.

RESULTS

Abortions

The frequency of spontaneous abortions, excluding the probands from the totals, was 15.5% for the first-cousin group and 13.6% for the controls (table 1). We have no explanation for the low value (7%) obtained in the second-cousin group, which differs from its control at the borderline level of significance ($P < .05$).

TABLE 1

MORBIDITY AND MORTALITY IN THE OFFSPRING OF FIRST-COUSIN, SECOND-COUSIN, AND UNRELATED PARENTS

	First Cousins	Unrelated Controls	Second Cousins	Unrelated Controls	Combined Controls
Families	58	58	27	27	85
Abortions*	31/200	27/198	8/115	12/80	39/278
Abortions (%)	15.5	13.6	7.0	15.0	14.0
Births	225	225	134	93	318
Stillbirths (%)	0.9	1.3	3.0	1.1	1.3
Sibs with same disorder as proband	17	14	18	4	18
Infant deaths†	19/217	9/221	12/130	2/91	11/312
Infant deaths (%)†	8.8	4.1	9.2	2.2	3.5
Mean socioeconomic level	38.7	44.9	35.7	46.1	45.3

* Total excludes probands.
† Excluding deaths due to same disorder as proband.

Infant Deaths (before 1 Year of Age)

Estimation of this value will be biased slightly downwards by inclusion of the proband; if the proband died from the condition by which he was ascertained, other possible causes of death would be obscured. However, this bias should be small. Exclusion of all probands, however, would bias the estimate upward. We have excluded from both numerator and denominator probands who died in the first year of life from the condition by which they were ascertained and sibs who died from the same condition (6 in the first-cousin group and 5 in the controls). The values for infant mortality are 8.8% vs. 4.1% for the first-cousin group and

its control ($P < .1$) and 9.2% vs. 2.2% for the second-cousin group and its control ($P < .1$). The difference between the combined consanguinity groups and the combined control groups is significant ($P < .01$). The causes of death in the first-cousin group were congenital malformations (3), birth injury (3), prematurity (1), bacterial infections (5, all before 1945), convulsions (1), no bone marrow (1), and unspecified (5). In the second-cousin group, the causes of death were birth trauma (2), pneumonia (3), meningitis (2), glycogen storage disease of the heart (2 sibs), diarrhea (1), convulsions (1), and absent adrenals (1). In the controls, the causes were diphtheria (1), accidental (2), and unknown (2).

Morbidity

A morbid disorder was defined as a medical or surgical condition severe enough to be a handicap if untreated. Disorders of clearly environmental origin were excluded, as were conditions that also occurred in the probands. In the first-cousin group, there were the following morbid disorders other than that by which the proband was ascertained: congenital heart disease (2), deafness (2), diaphragmatic hernia (1), rhizomelic spondylosis of Marie Strümpell (1), and multiple malformations not conforming to any recessively inherited condition known to us (2). In the controls, the morbid disorders were ventricular septal defect (1), pyloric stenosis (1), and a malformed head (2 sibs, probably anencephalics). The difference between the two groups (3.7% vs. 1.9%) is not statistically significant but is similar to those reviewed by Schull and Neel [1]. No recessive disorders were recognized in the first-cousin group or the controls, though one wonders if "no bone marrow" represents an inherited aplastic anemia. In the second-cousin group, two sibs of a proband with hidrotic ectodermal dysplasia had glycogen storage disease of the heart; the proband probably did too, though this was never proven. The "absent adrenals" occurred in a sib of an anencephalic proband.

DISCUSSION

These results are consistent with other surveys of consanguineous matings, suggesting that the risk of first cousins having a child with a disease known to show autosomal recessive inheritance is low. For instance, in the largest and best documented study of an unselected series of first-cousin matings in Japan [1], the frequency of recessively inherited diseases (as classified by us, from the diagnoses given) was about 0.9% compared to 0.1% in nonconsanguineous matings. However, these empirical estimates are often ignored in favor of calculations based on the number of lethal equivalents which are in turn based on comparisons of mortality in inbred vs. outbred populations [3]. Such calculations lead to estimates of one to three or more for the average number of lethal equivalents per individual. If these are (erroneously) translated into recessive lethal genes, the risk for a child of first-cousin parents developing a recessively inherited disease becomes 3%–9% or more, which we feel is probably too high.

The data on abortion support previous conclusions that there is no appreciable portion of recognizable fetal loss attributable to rare recessive genes [4–6].

For deaths in the first year of life (8.8% mortality for the first-cousin sample vs. 4.1% in the controls), our figures are similar to those of comparable studies. Böök [7] found a mortality of 8.5% in the first year for the offspring of Swedish first cousins as compared to 4% in the controls, while the corresponding figures for a French rural population were 9.1% and 4.4% [8] and for a Japanese population, 6.2 and 3.9% [6]. Slatis [5] found a mortality of 6.9% before age 1 month compared to 2.1% in the controls in an American urban population. For uncle-niece marriages and controls in Jerusalem, the mortality figures (age unspecified) were 16.8% and 6.7% [9].

However, it should be kept in mind that a significant proportion of infant deaths in some of these studies might not have occurred in a modern health care system. For instance, when our sample was divided into infants born before 1950 and those born in 1950 or later, the figures for mortality were 11% and 7.9% for the cousin group (first and second combined) and 4.7% and 2.6% for the control; a similar trend was noted by Yamaguchi et al. [5]. Since estimates of the number of lethal equivalents are based on differences in mortality between consanguineous and non-consanguineous matings, these data, if taken at their face value, show a change in the number of lethal equivalents since 1950.

This, and the fact that the infant mortality rates were similar in the first-cousin and second-cousin groups raised the question of whether the increased mortality in consanguineous matings might reflect differences in socioeconomic standing rather than the effects of recessive genes. We therefore classified our families according to a socioeconomic index devised for Canada [10]. The mean index was 37.8 for the combined cousin group and 45.3 for the controls ($P < .01$), suggesting that consanguineous matings tend to come from the lower socioeconomic groups which have higher morbidity and mortality rates. Similar differences have been noted in Japanese [1] and Indian [11] populations, though the Japanese data still demonstrated an inbreeding effect after adjustment for the socioeconomic differences. These two findings should remind us that estimates of lethal equivalents are valid only for the specific populations and specific environments that provided the data from which they were calculated. They should not be extrapolated uncritically to provide morbidity and mortality risks for particular first-cousin couples. In particular, they do not estimate the risk of having a child with a recessively inherited disease.

It would be interesting to know if data from other centers support the findings presented here.

SUMMARY

Effects of parental consanguinity on morbidity and mortality can be estimated from observations on families ascertained through a child with a disease or defect, provided that appropriate corrections are made for the ascertainment bias. The risk of first-cousin parents having a child with a recessively inherited disease appears to be low (< 1%). Data obtained by this approach suggest that the increased infant mortality associated with inbreeding (upon which calculations of lethal equivalents are based) may result in part from environmental differences between con-

sanguineous and nonconsanguineous matings, which may be changing. Thus estimates of the number of lethal equivalents in a population can change as the environment changes.

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